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Regeneration of skeletal muscle following eccentric injury

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Abstract

Eccentric contraction-induced skeletal muscle injuries, can be included in what is clinically referred to as muscle strains, are among the most common injuries treated in the sports medicine setting. Although patients with mild injuries often fully recover to their pre-injury levels, patients who suffer moderate or severe injuries can have a persistent weakness and loss of function that is refractory to rehabilitation exercises and currently available therapeutic interventions. The objectives of this review are to describe the fundamental biophysics of force transmission in muscle and the mechanism of muscle strain injuries, as well as the cellular and molecular processes that underlie the repair and regeneration of injured muscle tissue. The review will also summarize how commonly used therapeutic modalities affect muscle regeneration, and opportunities to further improve our treatment of skeletal muscle strain injuries.

Force Transmission and the Ultrastructure of Skeletal Muscle

Skeletal muscles consist of hundreds to thousands, and sometimes millions, of long, multinucleated fibers organized together by a highly ordered extracellular matrix (ECM). There are three general layers of ECM in muscles – the outermost layer is the epimysium, the intermediate layer is the perimysium and the inner most layer is the endomysium. The epimysium covers the surface of the muscle and has important roles in force transmission and insulation of the muscle [1]. Processes from the epimysium extend into muscle tissue and form the second layer of connective tissue, the perimysium. The perimysium contains blood vessels, nerves and lymphatic ducts, and structurally divides muscle fibers into functional groups called fascicles. The innermost layer of connective tissue is the endomysium. The endomysium is composed of two layers of mostly type I and type III collagen fibrils that fuse to form a sheet-like structure that inserts into the tendon [2]. The endomysium is important in gathering forces generated within the muscle and transmitting them to the tendon as well as laterally to other muscle fibers [3]. The endomysium is connected to a basement membrane that directly surrounds each muscle fiber and is composed mostly of type IV and VI collagen [2]. Unlike the fibrillar type I and type III collagen, type IV and VI collagen forms a mesh-like network that surrounds the muscle fiber [4]. An overview of the

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ultrastructure and major cellular components of muscle is presented in Figure 1, modified from Davis [5].

Forces that are generated from cross-bridge formation in the sarcomeres in fibers are transmitted through the cytoskeleton of the fiber, to a structure called the costamere that is embedded in the plasma membrane, or sarcolemma, of fibers [6–8]. The costamere transmits forces within the fiber to the collagen IV and VI molecules in the basement membrane, which then transmit forces to collagen I and III molecules in the endomysium [6–8]. The collagen I and III proteins in the endomysium then transmit forces longitudinally to the tendon, and laterally to the perimysium and epimysium [9]. The longitudinal transmission of force allows for locomotion, while the lateral transmission of force helps to dissipate the stress placed on individual muscle fibers; which, consequently reduces the likelihood of eccentric contraction-induced injuries to individual muscle fibers [10,11]. The orientation of type I and type III collagen in the muscle ECM is critical for the proper lateral transmission of force. Injuries to skeletal muscle often result in the formation of scar tissue that has a disordered organization of these molecules which then disrupts the efficient lateral transmission of force [12]. The greater risk for muscle trauma that occurs following an initial injury is therefore thought to be due to an accumulation of scar tissue within the muscle as well as a disruption of the lateral transmission of force between muscle fibers. Because of this, it is thought that preventing the accumulation of scar tissue is likely important in reducing the risk of re-injury.

Eccentric contraction-induced injuries to skeletal muscle tissue are among the most common conditions that are treated in the sports medicine setting [13–16]. Clinically, contraction-induced injuries are often referred to as muscle strains and are broken down into three categories. Mild (grade 1) contraction-induced injuries involve minor damage to muscle fibers and ECM, and patients will often make full recovery from these injuries [17]. Moderate (grade 2) contraction-induced injuries involve more substantial tears in muscle fibers and damage to the ECM.[17] Severe (grade 3) injuries are complete or near-complete tears across a cross-section of a whole muscle [17]. For patients that suffer from moderate and severe injuries, there is often a persistent atrophy of muscle fibers, an accumulation of fibrotic scar tissue in the ECM, and a decrease in strength, functional capacity and athletic ability [15,18,19]. These patients are also much more likely to have repeated muscle injuries, with each subsequent injury resulting in greater muscle atrophy and scar tissue deposition [15,19,20]. While preventing muscle atrophy and the accumulation of scar tissue could help to restore full strength and prevent re-injuries, our ability to prevent atrophy and fibrosis in sports medicine is currently limited [15,19,20].

Cellular Biology of Muscle Injury

Skeletal muscles can be injured when performing eccentric contractions [21]. The process of mechanical damage to sarcomeres is best explained in terms of the length-tension relationship of the sarcomere. The tension a muscle fiber can develop is proportional to the amount of overlap between the thick and thin filaments in a sarcomere [16,22,23]. Peak tension occurs when the muscle is at a length at which the maximum number of cross bridges can be formed. From this length, this is the point at which the load opposing the muscle contraction

is equal to the tension generated by the muscle, or an isometric contraction. As an actively contracting muscle is lengthened, the available cross bridge binding sites steadily decreases. The forces transmitted to the sarcomeres from the external load can damage the ultrastructure of the sarcomere, and this disruption of sarcomere ultrastructure can be responsible for the immediate decrease in force production following an injury [16,23–25]. In addition to damaging the sarcomeres, eccentric contractions can lead to disruption of the sarcolemma and endomysium due to shear forces generated during the contraction [26,27]. This process of sarcomere and membrane damage then initiates the subsequent muscle regeneration response.

The nuclei within skeletal muscle fibers have important roles in controlling the function of muscle fibers. Following injury to a muscle fiber, the nuclei in the damaged area often undergo apoptosis, and the failure to replace nuclei lost during injury may partially explain the persistent atrophy that is often observed in muscles that have suffered moderate and severe injuries [28,29]. A population of skeletal muscle stem cells, referred to as satellite cells or myoblasts, provide a source of new nuclei for injured muscle fibers [30]. Satellite cells reside in a space between the sarcolemma and the basement membrane and normally exist in a quiescent state [30]. In response to injury, satellite cells become activated, migrate to the site of damage, proliferate, coalesce into structures called myotubes and then fuse with the injured fiber to repopulate the nuclei lost as a result of injury [30]. A portion of the satellite cell pool will return to quiescence and will be able to respond to subsequent muscle injuries [30]. Satellite cells also play an important role in regulating the activity of fibroblasts, which are the cells chiefly responsible for ECM synthesis and remodeling [31].

In addition to satellite cells and fibroblasts, macrophages and neutrophils play important roles in muscle injury and regeneration. Neutrophils appear soon after the muscle is injured, help to initiate the inflammatory response, contribute to phagocytosis of damaged fibers and appear to help recruit macrophages to the site of injury [32]. As neutrophils are cleared from muscle, macrophages begin to accumulate [33]. Macrophages can be generally divided into two types. M1, or “classically activated” macrophages, produce proinflammatory cytokines and participate in the phagocytosis of the damaged tissue [34,35]. The M2, or “alternatively activated” macrophages, appear as M1 macrophages begin to decline, generally secrete anti-inflammatory cytokines and signaling molecules, and help to promote tissue repair and regeneration [32–35]. M2 macrophages can also increase satellite cell proliferation and fusion, promote myofibrillar protein synthesis, and increase general protein synthesis rates within muscle fibers [32–35]. An overview of the course of muscle regeneration following moderate muscle injuries is shown in Figure 2, modified from Faulkner [36].

Signaling Pathways that Modulate Muscle Hypertrophy and Atrophy

The molecular mechanisms that regulate skeletal muscle maintenance involve a complex sequence of interconnecting signaling pathways. Most of these signaling pathways can be classified roughly into one of two categories -- pathways that either activate protein synthesis and induce muscle hypertrophy, or pathways that activate protein degradation and induce muscle fiber atrophy [37,38]. Many of the growth factors and cytokines that activate these specific pathways can be found in an inactive form bound to regulatory proteins the

extracellular matrix surrounding muscle fibers, or in the circulation. These proteins can be activated in response to muscle injury, stretch, or exercise, and the interplay of these proteins coordinates the delicate balance between muscle growth and muscle wasting [37]. While there are hundreds of proteins and signaling molecules that regulate these processes, this review will discuss the selected factors that are important in muscle hypertrophy and atrophy. An overview of these pathways is presented in Figure 3.

The insulin-like growth factor 1 (IGF-1) pathway is thought to be one of the most important pathways that activate muscle hypertrophy in adult muscle fibers [37,38]. IGF-1, which can be induced in response to stimulation with growth hormone or after resistance exercise, binds to its receptor which activates a series of signaling molecules that eventually lead to activation of Akt and the mammalian target of rapamycin (mTOR) complex. mTOR can then activate ribosomal protein S6K of 70 kDa (p70S6K), which then initiates protein synthesis through the activation of ribosomes. IGF-1 can also promote the proliferation of satellite cells [37]. While the IGF-1 pathway is a well-known regulator of protein synthesis, recent work has identified the bone morphogenetic protein (BMP) pathway as another important regulator of muscle hypertrophy [39]. Members of the BMP pathway, specifically BMP-7, -13 and -14, which signal through the BMP receptors to activate the Smad-1, -5, and -8 proteins, can also potently induce muscle hypertrophy through the Akt signaling axis. Another important stimulus for protein synthesis is resistance exercise, which can activate the mTOR pathway independent of the IGF-1 or BMP pathways, although the specific receptors and signaling mechanisms that underlie this response are not yet fully understood [40].

Myostatin, or growth and differentiation factor 8 (GDF-8), is one of the central signaling molecules that induce muscle atrophy. Elevations in systemic myostatin lead to profound muscle atrophy, while animals that are genetically engineered to lack myostatin have an up to two-fold increase in muscle mass [41,42]. Upon binding to the activin receptors, myostatin activates the intracellular Smad-2 and -3 transcription factors that induce the expression of ubiquitin ligase enzymes, which target proteins for degradation via the ubiquitin proteasome system, leading to muscle atrophy [37–39]. The Smad-2/3 pathway is also able to inhibit protein synthesis, although the precise mechanisms are not well understood [39]. Recent work has also identified Activin A and B, GDF-11, and TGF-β, which activate the same signaling pathways as myostatin, as important and potent inducers of muscle atrophy [39,43–45]. Outside of muscle fibers, these signaling molecules also inhibit satellite cell proliferation, and promote fibroblast activity and collagen production [39,44,45].

Therapeutic Interventions for the Treatment of Skeletal Muscle Injuries

The treatment protocol for muscle injuries is often focused on reducing pain, inflammation and swelling in the acute phase, and once this phase has passed, to strengthen and improve range of motion of the injured muscle [46,47]. Numerous therapeutic modalities are used in the treatment of muscle strain injuries, despite a lack of evidence of effectiveness in the treatment of these injuries. This review will discuss basic and clinical research studies that have evaluated some of the modalities more commonly used in the treatment of muscle injuries in sports medicine, as well as new therapies that are on the horizon.

Cryotherapy and thermal ultrasound, which typically decrease or increase the temperature of muscle by 2–4°C, are among the most popular modalities used in the treatment of muscle injuries are [48–50]. Ice and other forms of cryotherapy are commonly used in the acute muscle injury phase to cool muscle tissue, provide analgesia, and are thought to alter cellular metabolism, reduce inflammation and oxidative stress in the injured tissue [48,50,51]. Thermal ultrasound is frequently used in rehabilitation sessions to warm tissue after the acute inflammatory phase has passed, and is suspected to promote the healing of tissue by increasing local blood flow, increasing oxidative metabolism and inducing protein synthesis [50,52,53]. In addition to the thermal effects of ultrasound, acoustic cavitation forces are also thought to impact the biological activity of cells [50,52,53]. While these mechanisms are commonly taught to students in rehabilitation and medical training, and help to shape how these modalities are applied clinically, there is very little objective, evidence-based information on how the therapeutic application of cold and heat changes biological processes in human skeletal muscle.

Most of our knowledge in this area comes from in vitro studies, or studies of animal models of muscle injury. Decreasing the temperature of cultured satellite cells cells by 5°C under normal 37°C culture conditions reduces their proliferation rate, but also decreases apoptosis, or programmed cell death [54]. In rats subjected to an ischemia/reperfusion muscle injury, cryotherapy applied three hours after the injury reduces neutrophil accumulation and reactive oxygen species formation, and enhances the metabolic function of mitochondria [55]. In a rat muscle crush-injury model, however, reducing the temperature of muscle by 12°C for 20 minutes after inducing the injury results in reduced inflammation in the acute phase, but delayed muscle regeneration in the long term [56]. When muscle stem cells are warmed by 5°C over their normal 37°C temperature in vitro, their proliferation rate is increased, but so is the amount of apoptosis [54]. In muscle cells cultured from chicks, the application of therapeutic ultrasound in vitro results in elevated progenitor cell proliferation and an increase in the size of differentiated myotubes [57]. In vivo, high-dose therapeutic ultrasound that warms tissue by over 10°C can activate the HSP70 gene promoter, which is a heat and inflammation sensitive gene, in rats [58]. Lower doses of ultrasound delivered to mouse muscle, that result in an increase in tissue temperature of 4–5°C, surprisingly triggered the infiltration of immune cells and an upregulation in numerous proinflammatory cytokines like IL-1β, MCP-1 and TNF-α [59]. While these in vitro and in vivo animal model studies have been somewhat informative, and would generally be predicted to reduce muscle regeneration and impair force production, often times the dose and extent of the cryotherapy or thermal ultrasound is much greater than what is used clinically, making it a challenge to directly apply these findings to patients. There have been some descriptive epidemiological studies that have looked at cryotherapy and thermal ultrasound in patients with muscle injuries, but these studies have produced conflicting results on the efficacy of these modalities in improving patient outcomes [48,49,53,60–62]. Further animal studies using more clinically relevant temperature changes and larger epidemiological studies in patients with muscle strain injuries, could further enhance the evidence-based application of these modalities in the sports medicine setting.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are commonly used in the treatment of muscle strain injuries [63]. NSAIDs exert their action by inhibiting cyclooxygenase (COX)

enzymes from producing prostaglandins, which are small lipid species derived from the fatty acid, arachadonic acid. There are three isoforms of the COX enzymes. COX-1 is constitutively active in all tissue and produces prostaglandins that serve in basal physiologic functions. COX-2 is an inducible enzyme, expressed only after activation producing prostaglandins involved in inflammation. COX-3 is another isoform that appears to be active generating cytokines necessary for fever production [64,65]. Numerous prostaglandins are produced by the COX enzymes, and they have diverse roles in mediating inflammation, nociception, protein synthesis and many other physiologic processes [15,63,64]. While NSAIDs are commonly used in the treatment of muscle strains and are generally effective in treating the pain associated with these injuries, numerous studies have shown that blocking the COX enzymes after muscle injury generally inhibits biological processes associated with muscle regeneration, leading to long term deficits in muscle function. The inhibition of either or both COX-1 and -2 reduces the proliferation, and differentiation and fusion of cultured satellite cells [64]. At the whole muscle level, in animal models of muscle injury, NSAID use can result in an initial reduction in inflammation, but also leads to smaller, weaker muscle fibers and greater connective tissue accumulation in the long term [63,66]. Data from human resistance training studies have demonstrated that use of NSAIDs blunt muscle hypertrophy, through preventing the production of prostaglandin $F_{2\alpha}$ which induces Akt/mTOR signaling [67]. In addition to the COX enzymes, 5-lipooxygenase (5-LOX) is another fundamental enzyme in the inflammatory cascade that occurs after muscle injury. 5-LOX also uses arachidonic acid as a substrate, but produces various classes of leukotrienes that also can promote inflammation and regulate immune function, similar to prostaglandins [68]. COX enzyme inhibition can shunt arachidonic acid to the 5-LOX pathway and increase the production of leukotrienes, and this increase in leukotriene production is thought to be one of the factors that causes side effects from the use of COX inhibitors [69]. The use of licofelone, which is a combined COX/LOX inhibitor, results in a reduction in fibrosis and fat infiltration after rotator cuff muscle injury [70]. While licofelone offers some improvements over traditional NSAIDs in promoting muscle regeneration, it does not improve muscle force production [70]. Numerous next generation anti-inflammatory compounds that can selectively inhibit the production of specific pro-inflammatory prostaglandins are in the pipeline of drug development and clinical trials testing. Within the next ten years it is possible that new pharmacological therapies will be available to selectively block pain and inflammation without decreasing tissue regeneration.

Platelet-rich plasma (PRP) is an experimental therapy that is gaining in popularity for the treatment of soft tissue injuries in sports medicine. PRP is a biologically active component of whole blood containing platelets, growth factors, cytokines and various other enzymes [71]. Controlled laboratory studies using animal models of muscle injury have displayed mixed results regarding the use of PRP. In a rat eccentric muscle strain injury model, compared to platelet poor plasma (PPP), PRP improves histological signs of muscle regeneration and decreases the time to recover full strength after injury [72]. However, in a blunt force contusion injury model in rats, PRP treatment does not improve force production compared to controls [73]. In cultured connective tissue fibroblasts, PRP turns on several pro-inflammatory pathways, including the potent TNF-α/NFκB pathway [74]. While the mechanism of action of PRP is not entirely clear, PRP may work in chronic injuries by

triggering an acute bout of inflammation that is followed by a regenerative response [74]. Although the utilization of PRP is gaining popularity, based on the mixed results of these small-scale laboratory studies and the lack of any large scale clinical trials [71], there continues to be little evidence to support PRP use in the treatment of muscle strain injuries.

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Abbreviations

5-LOX	5-lipooxygenase
Akt	Protein Kinase B Alpha
BMP	Bone morphogenetic protein
COX	Cyclooxygenase
ECM	Extracellular matrix
GDF	Growth and differentiation factor
HSP70	Heat shock protein-70
IGF-1	Insulin-like growth factor-1
IL-1β	Interleukin-1-beta
MCP-1	Monocyte Chemotactic Protein-1
mTOR	Mammalian target of rapamycin
MuRF-1	Muscle ring finger-1
MUSA-1	Muscle ubiquitin ligase of SCF complex in atrophy-1
NFκB	Nuclear factor kappa-b
NSAID	Non-steroidal anti-inflammatory drug
p70S6K	Ribosomal protein S6K of 70 kDa
PRP	Platelet rich plasma
Smad	Mad-Related Protein
TGF-β	Transforming growth factor-beta
TNF-α	Tumor necrosis factor-alpha

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Summary

Skeletal muscle strain injuries are among the most common injuries treated in the sports medicine setting. While patients with mild injuries often recover, there can be a persistent atrophy and loss of function for moderate and severe muscle injuries. The physiological processes behind the repair and recovery of injured muscles involves coordinated efforts between multiple cell types, including muscle fibers, satellite cells, fibroblasts, and various immune cells. For many of the therapeutic modalities used to treat muscle injuries, there is either a lack of evidence to guide their use, or evidence that suggests they may be detrimental to the rehabilitation process. While we have a fairly good understanding of the basic cellular, molecular and biochemical processes that underlie muscle hypertrophy and atrophy, there is a need to perform further research to guide the evidence based use of current therapeutic modalities, and to identify new therapies to enhance the recovery of skeletal muscle from strain injuries.

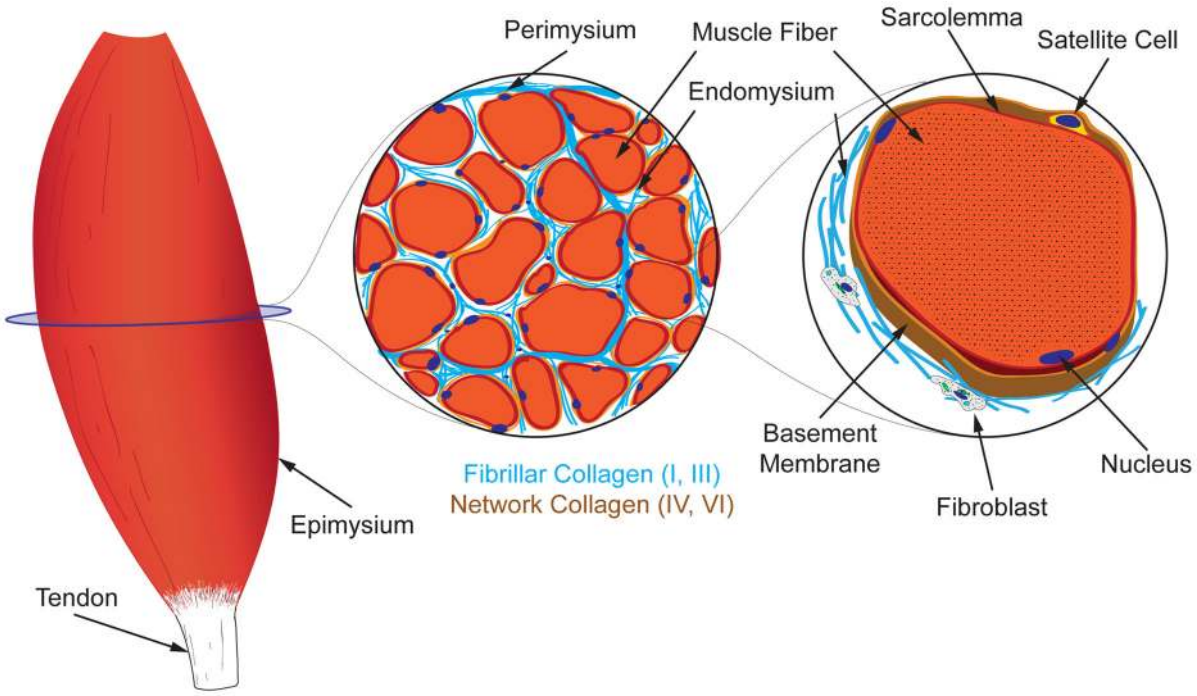

Figure 1.

Overview of the ultrastructure of skeletal muscle, demonstrating the interaction between different cell types and their surrounding matrixes. Figure modified from Davis [5].

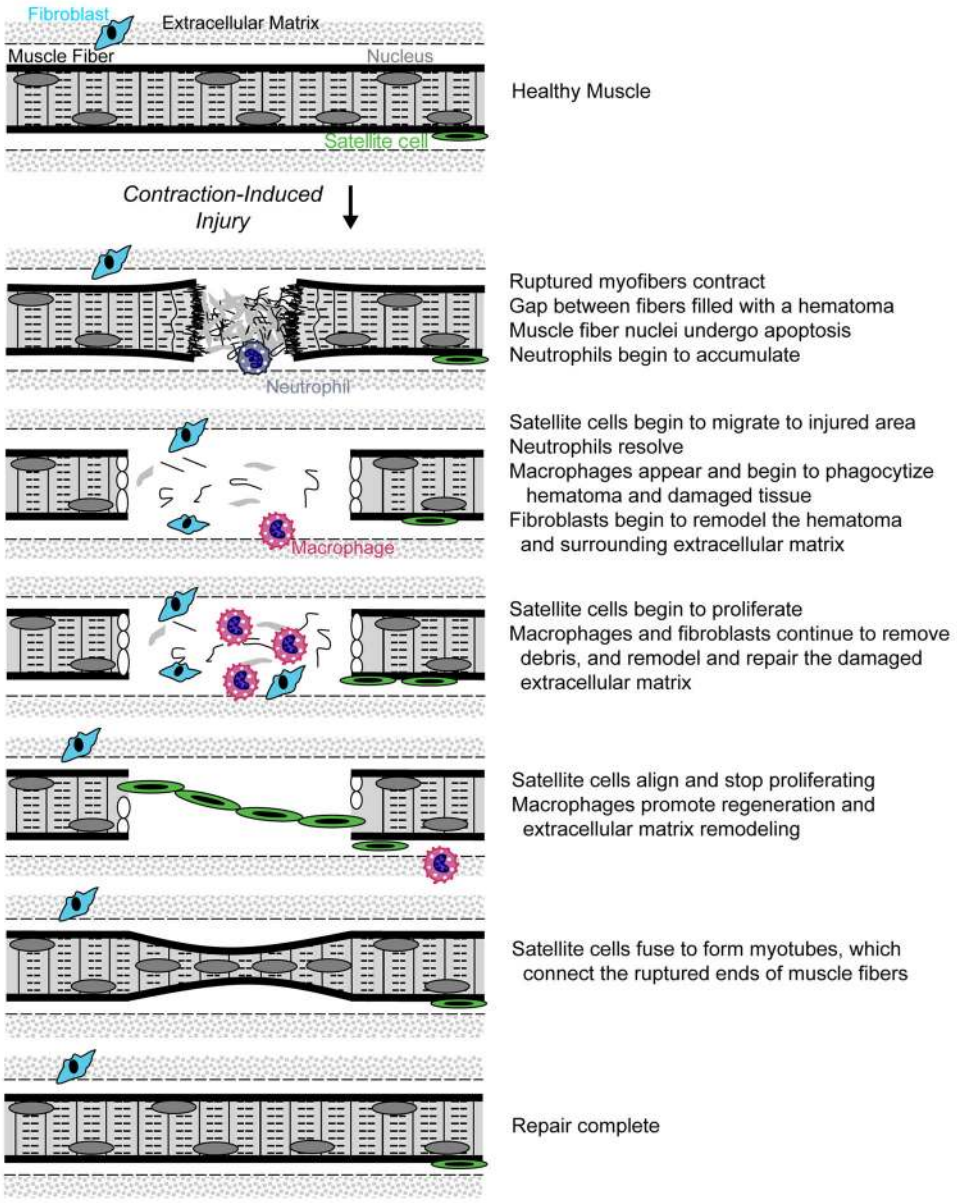

Figure 2.

Overview of the cellular processes of skeletal muscle repair. Figure modified from Faulkner [36].

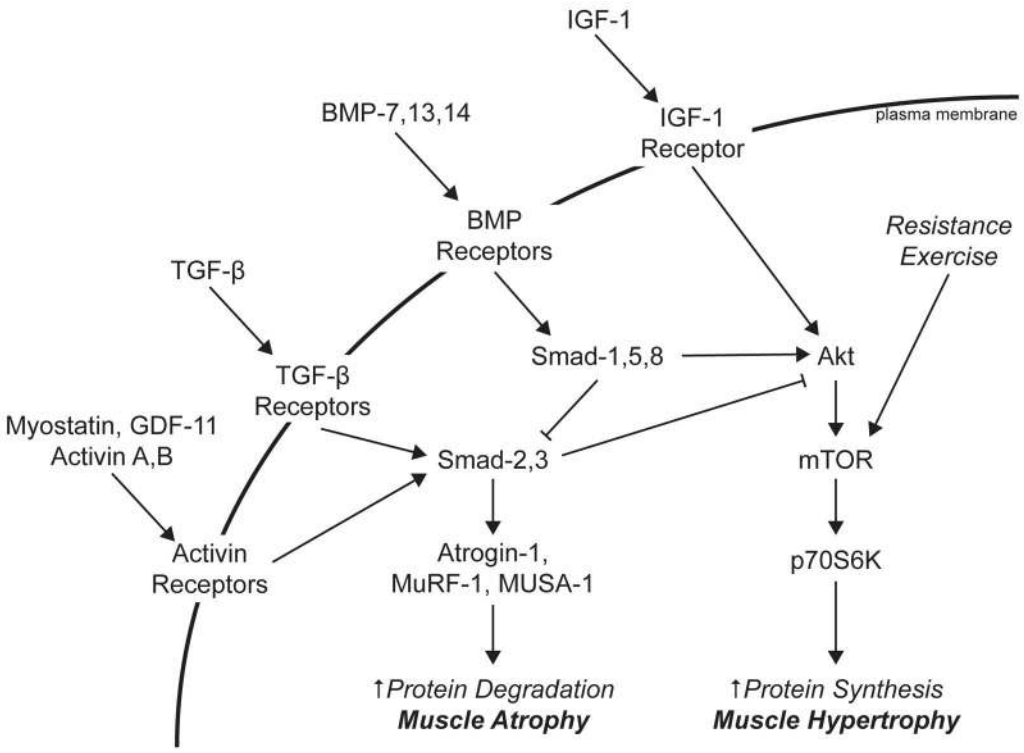

Figure 3.
Overview of selected signaling pathways that regulate skeletal muscle hypertrophy and atrophy.